# Timed-Sequential Induction Therapy Improves Postremission Outcome in Acute Myeloid Leukemia: A Report From the Children's Cancer Group

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**Timed sequencing of cycles of induction chemotherapy in acute myeloid leukemia (AML) has been proposed as a way to achieve maximal leukemic cell kill through recruitment and synchronization of residual neoplastic cells. Furthermore, whether intensive induction therapy should be continued in the presence of profound myelosuppression is an important question. The Children's Cancer Group (CCG) conducted a prospective randomized trial in which 589 patients with AML were randomized at diagnosis to one of two induction approaches involving a 4-day cycle of five active chemotherapeutic agents, with the second cycle administered either 10 days after the first cycle, despite low or dropping blood counts (intensive timing), or 14 days or later from the beginning of the first cycle, depending on bone marrow status (standard timing). All patients achieving remission received a total of four cycles of induction therapy. They were then allocated to allogeneic bone marrow transplantation (BMT) if a compatible family donor was present or randomized to aggressive nonmyeloablative therapy or to myeloablative therapy with purged autologous BMT rescue. The three postremission arms remain coded. Induction success and median days to complete induction were similar for the 295 patients randomized to the intensive timing arm (75%, 99 days) compared with the 294 patients randomized to the standard timing arm (70%, 105 days; $P = .18$ for remission). However, a marked improvement in outcome was demonstrated in patients randomized to the intensive timing arm, with an actuarial event-free survival at 3 years of 42% ± 7% (95% confidence interval [CI]) versus 27% ± 6% for patients on the standard timing arm ($P = .0005$). Disease-free survival results at 3 years from the end of induction were superior for patients receiving intensively timed induction therapy (N = 211), 55% ± 9% versus 37% ± 9% for standard timing patients (N = 195, $P = .0002$), with a median follow-up from achieving remission of 28 months. Superior results were documented for patients receiving intensive timing irrespective of the postremission therapy to which they were allocated. Intensively timed induction therapy for patients with AML markedly improves event-free survival, even for patients undergoing myeloablative therapy with BMT rescue. Without controlling for the type of induction therapy received, results of various BMT studies in AML comparing different preparative regimens will be difficult to interpret.**


ACUTE MYELOID leukemia (AML) in both children and adults requires intensive, myelosuppressive induction therapy for achieving a remission and further postremission therapy for durable long-term survival. Improvement in both induction success and long-term outcome has been slow but consistent over the last 20 years.[1,2] More aggressive induction chemotherapy has led to remission success in 70% to 85% of patients so treated, but at a price; namely, increased morbidity and mortality from prolonged myelosuppression.[3-6] Similarly, postremission approaches appear to improve with the intensity of therapy.[7,8] The ultimate intensity has been achieved by administering myeloablative chemotherapy and/or radiation followed by autologous or allogeneic bone marrow transplantation (BMT) rescue.[9-11] Morbidity and mortality associated with BMT are high but considered worth the risk for the potential benefit of long-term disease-free survival (DFS).

There is interesting in vitro evidence in AML that, after an initial exposure to cytotoxic agents, leukemia cells can be recruited synchronously into the cell cycle, thus rendering them potentially more sensitive to cell cycle-specific agents if re-exposed at a particular time.[12-15] Maximum recruitment appears to occur approximately 6 to 10 days after the initial chemotherapy exposure. In a follow-up of preclinical studies,[14] investigators at Johns Hopkins University showed that patients with AML receiving either one or two intensively timed rounds of chemotherapy could have prolonged DFS with no further treatment.[16-18] Capizzi et al[19] then showed that the use of high doses of cytarabine with L-asparaginase administered 7 days apart was quite effective in inducing remissions in patients with poor-risk AML. In sequential Children's Cancer Group (CCG) studies, an intensive timing approach improved long-term outcome when used in the postremission phase and obviated the need for additional maintenance therapy in children with AML.[3,20]

For induction therapy in AML, the question of whether intensity of treatment affects long-term outcome rather than just remission success has never been rigorously tested. This concept has important implications as investigators treating patients with AML are often faced with whether or not to continue intensive therapy in the face of profound myelosuppression. Specifically, is the added myelosuppression at such a point worth the risk of further prolongation of pancytopenia?

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In this CCG study, children with AML were randomized at diagnosis to either a sequentially timed or standard induction approach. A 4-day cycle of five active chemotherapeutic agents was followed by a second cycle administered either 10 days after the first cycle, despite low or dropping blood counts and other side effects of therapy (intensive timing), or 14 days or later from the beginning of the first cycle, depending on BM status (standard timing). The results show that patients receiving intensively timed induction therapy have a superior outcome, irrespective of the type of postremission therapy received.

## PATIENTS AND METHODS

CCG-2891 opened in October 1989, and the randomization between standard timing and intensive timing induction therapy closed in May 1993. Eligibility included all children and adolescents less than 21 years of age with blood and marrow biopsy confirmation of the diagnosis of French-American-British (FAB) AML types MO to M7,[21] acute undifferentiated or biphenotypic leukemia with evidence of myeloid differentiation noted on cytologic examination; myelodysplastic syndrome (MDS); or granulocytic sarcoma (chloroma). Patients with acute promyelocytic leukemia (APL; M3) became eligible for the Intergroup APL Study (INT 0129; CCG-2911) once that study opened in April 1992. Patients with known Fanconi anemia or those with Philadelphia chromosome-positive chronic myeloid leukemia in the chronic phase were excluded. Seven patients were deemed to be ineligible after central review showed a diagnosis other than those noted above. Six hundred eighty-six patients were eligible. In an attempt to define a group of children that would parallel AML in young and middle-aged adults, the following patients were excluded from analysis in this report: (1) patients with Down syndrome as a predisposing factor (n = 55); (2) patients with AML as a second malignant neoplasm (n = 9); (3) patients with granulocytic sarcoma and no evidence of BM involvement (n = 14); and (4) patients with de novo MDS (n = 19). The remaining patients (589 total) form the basis of this report. The other four subgroups not analyzed here will be reported separately.

Patients and family members were requested to undergo HLA-A, B, and DR typing at the time of AML diagnosis. Patients and/or families signed consent forms before participation in the study, and the protocol was approved by each participating CCG member's institutional review board. The study has been regularly evaluated by a Data Monitoring Committee.

*Induction therapy.* Patients on CCG-2891 received a five-drug cycle of induction therapy administered over 4 days: dexamethasone, cytarabine, 6-thioguanine, etoposide, and daunorubicin (DCTER; Table 1). This chemotherapy regimen used the identical drugs at equal or higher concentrations to those used in the previous CCG study, CCG-213, in a regimen called Denver.[3] Because Denver therapy in standard timing was known to be associated with acceptable induction rates (76%) and excellent long-term event-free survival (EFS; 35% ± 5% at 3 years), it was used in CCG-2891 in a slightly modified form. Daunorubicin, cytarabine, and etoposide were all administered as a continuous infusion mixed in the same intravenous (IV) bag as previously described[22] for 96 hours. IV bags were changed daily, with stability of the three drugs mixed together documented for at least 24 hours.[22] Patients randomized to intensive timing received a second obligatory cycle of DCTER therapy identical to cycle no. 1 after a 6-day rest, irrespective of BM and/or hematologic status. Delays of 2 to 4 days were permitted for patients who experienced severe ileus or other life-threatening events with cycle no. 1. Patients randomized to standard timing therapy had a BM examination, including biopsy on day 14. If there was evidence of clearing of circulating blasts and a hypoplastic marrow indicating a large leukemia kill from the first cycle, cycle no. 2, identical to cycle no. 1, was held until the patients' blood counts recovered and/or there were clear signs of leukemia progression. Patients with residual leukemia documented on day 14, defined as greater than 40% blasts in a mildly hypocellular to hypercellular marrow, received cycle no. 2 at that time.

For patients on either induction arm, BM biopsies and aspirates were performed starting 14 to 28 days after the beginning of cycle no. 2. Individuals showing no leukemia response were considered protocol failures and went off study, continuing for follow-up. Those who showed a response, but whose marrows remained hypocellular with pancytopenia, waited until criteria for either residual leukemia or remission (absolute neutrophil count $\geq$1,000/$\mu$L and platelet count of $\geq$100,000/$\mu$L, with $<$5% blasts in a recovering BM) were found. Patients then received the second two cycles of therapy as consolidation in an intensive or standard fashion, based on initial randomization. Marrow and peripheral blood count status were determined, with those patients exhibiting residual leukemia removed from the study. Hence, all children proceeding to the postremission treatment phase received four cycles of DCTER therapy, regardless of whether they were in remission after the first two cycles and whether they received intensive or standard timing.

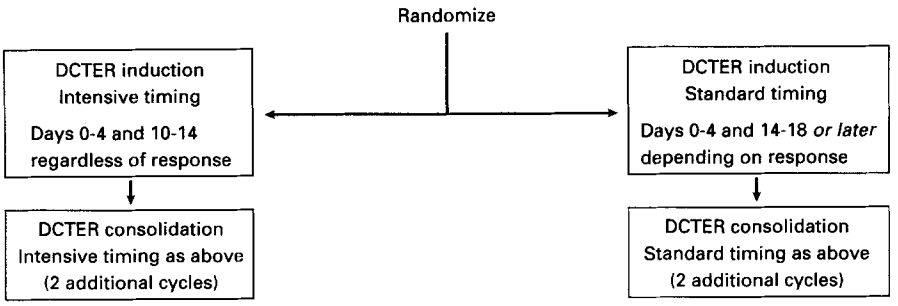
For patients in remission after four DCTER cycles, those with five- or six-antigen HLA-matched, mixed leukocyte culture (MLC)-compatible family donors were allocated to allogeneic BMT. All others were eligible for BM harvesting with 4-hydroperoxycyclophosphamide (4-HC) ex vivo purging as previously described.[23,24] These patients were randomized between intensification therapy requiring autologous BMT rescue versus intensification including intensively timed high-dose cytarabine (see below).

*Postremission phase.* Patients allocated to allogeneic BMT or those randomized to autologous BMT received a preparative regimen at a CCG-certified BMT center consisting of 4 days of oral busulfan and 4 days of cyclophosphamide (Table 1). Allogeneic or autologous marrow was infused after a 1-day rest. For patients undergoing allogeneic BMT, graft-versus-host disease (GVHD) prophylaxis consisted of 15 mg/m$^2$ methotrexate IV on day 1 followed by 10 mg/m$^2$ on days 3, 6, and 11 and weekly until day 100. Treatment of acute and/or chronic GVHD and supportive care approaches were left to the option of the individual transplantatation center. After recovery from the BMT procedure, patients were observed with no further therapy.

For patients randomized to more conventional chemotherapy not requiring BMT rescue, treatment consisted of four total courses of three different chemotherapy regimens, each lasting approximately 1 month (Table 1). Course 1 consisted of a high-dose cytarabine regimen based on that of Capizzi et al[19] and used in previous CCG studies.[3,20] Once hematologic recovery had occurred, patients received the second and third courses of therapy consisting of 28-day cycles, with daily 6-thioguanine the centerpiece, identical to the maintenance therapy administered in four previous CCG studies.[3,20,25,26] The fourth course of postremission therapy consisted of a 5-day pulse of daunorubicin, cytarabine, etoposide, 6-thioguanine, and dexamethasone.[3,20] After the four courses of postremission therapy, patients were observed with no further treatment. Results from the three postremission arms remain coded (regimens X, Y, and Z) at this time. Because additional patients were needed to satisfy prestudy sample size estimates for answering the postremission questions, patients enrolled on CCG-2891 after May 1993 received a common induction arm with ongoing allocation to the three postremission arms.

*Other therapeutic considerations.* All patients enrolled on CCG-2891 had lumbar punctures performed at diagnosis, with intrathecal cytarabine administered at the start of each DCTER cycle (4 doses).

**Table 1. CCG-2891 Therapy**




Day 0 through 4: DCTER induction
**D**examethasone 6 mg/m$^2$/d (0.2 mg/kg/d) thrice daily
**C**ytarabine 200 mg/m$^2$/d (6.7 mg/kg/d) continuous infusion
**T**hioguanine 100 mg/m$^2$/d (3.3 mg/kg/d) twice daily
**E**toposide 100 mg/m$^2$/d (3.3 mg/kg/d) continuous infusion
**R**ubidomycin (daunorubicin) 20 mg/m$^2$/d (0.67 mg/kg/d) continuous infusion
Cytarabine intrathecal (age-based doses)

**Postremission Therapy**

1. Patients randomized to conventional chemotherapy
   A. Course 1: Days 0 through 2 cytarabine, 3 g/m$^2$/dose (100 mg/kg) IV over 3 h every 12 h × 4 doses. L-asparaginase 6,000 IU/m$^2$ (200 IU/kg) IM, hour 42. Days 7 through 9 cytarabine and L-asparaginase repeated exactly as administered days 0 through 2.
   B. Courses 2 and 3: Two 28-day cycles of 75 mg/m$^2$ 6-thioguanine (2.5 mg/kg) PO daily, days 0 through 27; 1.5 mg/m$^2$ vincristine (0.05 mg/kg) IV, day 0; 75 mg/m$^2$ cytarabine (2.5 mg/kg) IV everyday × 4, days 0 through 3; 75 mg/m$^2$ cyclophosphamide (2.5 mg/kg) IV everyday × 4, days 0 through 3; 100 mg/m$^2$ 5-azacytidine (3.3 mg/kg) IV everyday × 4, days 0 through 3.
   C. Course 4: 25 mg/m$^2$/dose cytarabine (.83 mg/kg) SQ or IV every 6 h × 5 days, days 0 through 4; 30 mg/m$^2$ daunorubicin (1 mg/kg) IV day 0; 150 mg/m$^2$ etoposide (5 mg/kg) IV/dose × 2, days 0 and 3; 50 mg/m$^2$/dose 6-thioguanine (1.67 mg/kg) orally every 12 h × 5 days, days 0 through 4; 2 mg/m$^2$/dose dexamethasone (.067 mg/kg) orally every 8 h × 4 days, days 0 through 3.

2. Patients allocated to allogeneic or randomized to autologous BMT. Pre-BMT preparative regimen:
   A. Busulfan 1 mg/kg/dose, administered orally every 6 h × 16 doses, days −9 to −6.
   B. Cyclophosphamide 50 mg/kg/d IV over 1 h daily × 4 days, days −5 to −1.

Doses in parentheses were used for children less than 3 years of age. If a leukemic response was documented, all patients received DCTER cycles 3 and 4 in an intensive or standard fashion, based on initial randomization, after marrow recovery.

For those with central nervous system (CNS) meningeal leukemia at diagnosis (defined as ≥5 cells/μL with blasts present), intrathecal cytarabine was in addition administered twice a week for a total of six doses. Details of CNS prophylaxis and treatment, including that for patients with refractory or recurrent disease, have been previously reported.[24]

Radiation therapy was considered for all patients who presented with or developed granulocytic sarcomas. Patients were to receive radiation therapy to the local mass sometime after the first two cycles of induction therapy. Radiation could be performed earlier for mass lesions leading to symptoms requiring immediate intervention. The recommended radiation dose was 20 Gy in 10 divided doses with a 1-cm margin.

The use of hematopoietic growth factors was not allowed in this study, except for the use of granulocyte-macrophage colony-stimulating factor (GM-CSF) for poor engraftment after BMT.

*Required observations.* Patients who entered this study had several items recorded, including a detailed history and physical examination at the time of diagnosis; complete blood counts; lumbar puncture; BM examination; various coagulation and chemistry studies; HLA typing of patient, parents, and siblings; and baseline cardiac evaluation, including ECG and echocardiogram. The initial BM aspirate was studied for cytochemistry, chromosomal analysis, and immunophenotyping with monoclonal antibodies, with central review of each parameter. Subsequent BM aspirations and biopsies were required based on induction regimen received and response. Toxicity associated with leukemia and its treatment was recorded, including infectious episodes and various organ toxicities—hematopoietic, gastrointestinal, hepatic, renal, cardiac, and CNS.

*Statistical considerations.* Analyses of data obtained in this study through January 1995 were performed with the use of several standard methods. Results were calculated as of the day of last contact, with a cut-off of July 1, 1994. Accrual goals were determined before initiation of the study, with the power to detect a 10% difference in DFS at 2 years between the two induction arms of 0.88.

For the initial randomization, patients less than 2 years of age were stratified on FAB morphology (M5 histology versus all others). For the postremission randomization, patients were stratified according to induction regimen received.

Differences in survival and DFS from the end of induction therapy and in survival and EFS from the time on study were tested for significance using the log rank statistic.[27] Patients lost to follow-up were censored at their last known point on study. Survival rates were estimated by the method of Kaplan and Meier and confidence intervals for these methods were calculated using Greenwood's formula.[28] The significance of observed differences in proportions was tested using the $\chi^2$ statistic and Fisher's exact test when appropriate for small samples. All reported comparisons were based on regimens to which patients were allocated or randomized (intent to treat).

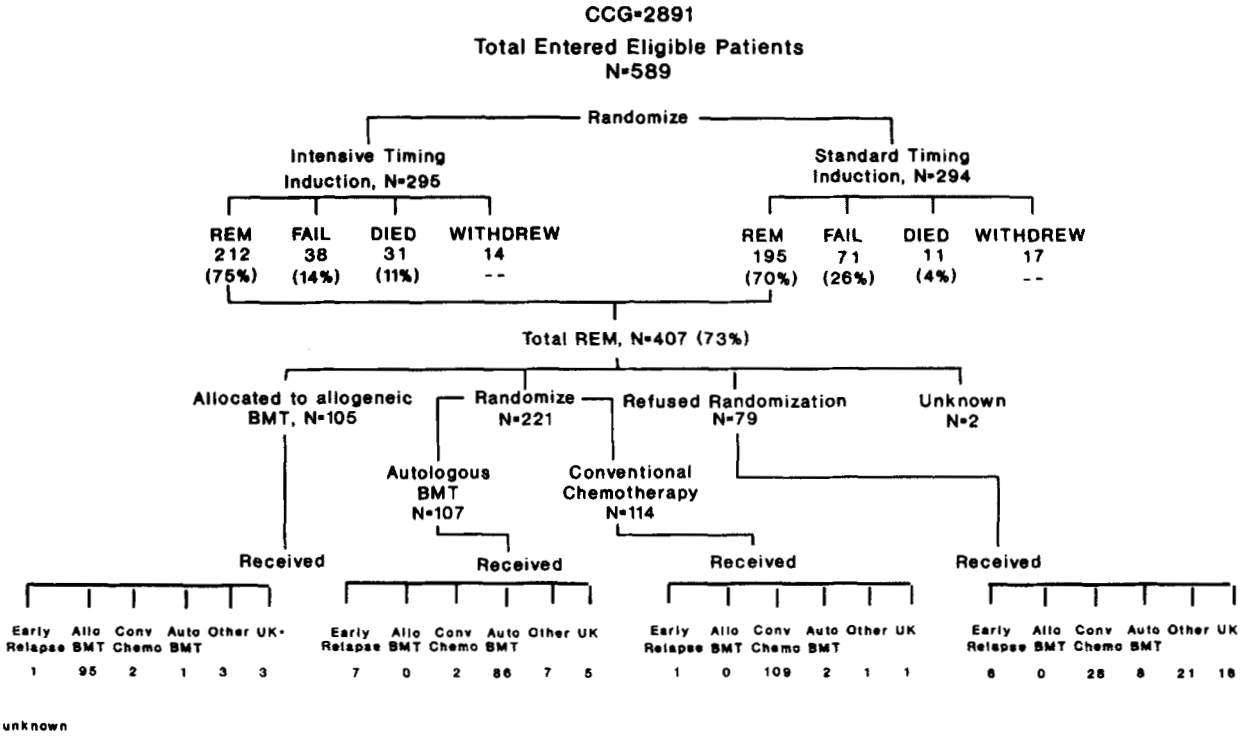



**Fig 1. Flow of patients entered onto CCG-2891, including compliance with postremission therapy allocation and randomization.**

Comparisons were also made for regimens actually received, but no important differences were found between these analyses and those based on the more standard approach noted above. Hence, only the intent-to-treat analyses will be reported.

## RESULTS

*Study logistics and patient characteristics.* There were 589 eligible patients randomized on this study, 295 to the intensive timing arm and 294 to the standard timing arm (Fig 1). Compliance with the induction randomization was greater than 98% in both arms. Thirty-one patients withdrew before induction success could be determined. Reasons for withdrawal included parental or physician choice, usually because of toxicity or concerns that the first course of therapy was ineffective. Of 558 patients who were evaluable, 407 subsequently completed the induction phase in remission. One hundred five patients were allocated to allogeneic BMT based on an HLA-matched sibling or parent donor, 114 patients were randomized to conventional chemotherapy, and 107 to autologous BMT (N = 326). Seventy-nine patients refused randomization, and data are unavailable in the remaining 2 patients. Figure 1 documents the actual compliance with the regimens to which patients were allocated or randomized and outcome for the induction regimens.

Characteristics of patients analyzed as part of this study are listed in Table 2, including age, white blood cell count (WBC), and FAB subtype at diagnosis. Comparisons for these three variables, which have shown some prognostic significance in previous CCG trials,[1] were made for patients randomized to the two induction arms. No statistical differences were noted for ages of 0 to 2 years versus ages of 3 to 10 years versus ages of 11+ years ($P$ = .51); WBC as a continuous variable ($P$ = .58); FAB subtypes ($P$ = .59); and all other variables listed in Table 2. There were also no significant differences in the percentage of patients with various cytogenetic abnormalities that may have affected outcome, such as −7, 11q23 rearrangements, 16q22 abnormalities, +8, or t(8;21) (Table 2). Finally, there were no differences in the rate of deaths during the first 10 days of study, indicating equal adverse performance status at diagnosis for patients on both arms (Table 2).

*Induction outcome.* Overall, 426 patients (74%) achieved remission after the first course (2 cycles) of DCTER therapy, and an additional 27 patients (5%) recovered peripheral blood counts but had residual leukemia. Four hundred seven patients (73%) remained alive in remission after all four cycles of induction therapy. There were 42 deaths (8%) secondary to leukemia or its treatment, and 109 patients did not achieve remission (20%). Reasons for not achieving remission differed between the intensive timing and standard timing arms (Fig 1). For patients on the intensive timing arm, 75% achieved remission, with half who did not achieve remission dying of toxicity (11%) and half showing a lack of leukemia response (14%). Seventy percent of patients randomized to standard induction timing achieved remission, with only 4% dying from toxicity but 26% with refractory leukemia. Although there are no statistical differences in the total number of patients achieving remission ($P$ = .18), there was a significantly higher number of patients failing to respond to induction therapy on the standard arm ($P$ = .0003)

**Table 2. Characteristics of Patients Included in This Study (CCG-2891; N = 589)**

| | Intensive Timing (N = 295) | | Standard Timing (N = 294) | | | | |
|---|---|---|---|---|---|---|---|
| | No. | (%) | No. | (%) | Total | (%) | *P* Value |
| Age (yr) | | | | | | | |
| 0-2 | 55 | (19) | 60 | (20) | 115 | (20) | |
| 3-10 | 118 | (40) | 126 | (43) | 244 | (41) | |
| 11-21 | 122 | (41) | 108 | (37) | 230 | (39) | .51 |
| WBC (/μL) | | | | | | | |
| Median | 20,400 | | 20,400 | | 20,400 | | |
| Range | 500-575,000 | | 700-644,400 | | 500-644,400 | | .58 |
| FAB Subtype | | | | | | | |
| M1 | 36 | (14) | 41 | (15) | 77 | (15) | |
| 2 | 71 | (27) | 79 | (30) | 150 | (28) | |
| 3 | 26 | (10) | 29 | (11) | 55 | (10) | |
| 4 | 69 | (26) | 63 | (24) | 132 | (25) | |
| 5 | 40 | (15) | 39 | (15) | 79 | (15) | |
| 6 | 6 | (2) | 9 | (3) | 15 | (3) | |
| 7 | 15 | (6) | 7 | (3) | 22 | (4) | |
| Unknown, other | 32 | — | 27 | — | 59 | — | .59 |
| Cytogenetics | N = 165 | | N = 148 | | N = 313 | | |
| Normal | 39 | (24) | 37 | (25) | 76 | (24) | .88 |
| 11q23 abnormality | 20 | (12) | 25 | (17) | 45 | (14) | .30 |
| t(8;21) | 15 | (9) | 16 | (11) | 31 | (10) | .75 |
| t(15;17) | 16 | (10) | 12 | (8) | 28 | (9) | .77 |
| 16q22 abnormality | 10 | (6) | 12 | (8) | 22 | (7) | .63 |
| +8 | 15 | (9) | 10 | (7) | 25 | (8) | .58 |
| −7/7q− | 6 | (4) | 8 | (5) | 14 | (5) | .63 |
| Other characteristics at AML diagnosis | | | | | | | |
| Granulocytic sarcoma | 21 | (7) | 18 | (6) | 39/584 (7) | | .74 |
| Skin infiltrate | 12 | (4) | 23 | (8) | 35/588 (6) | | .08 |
| Gum hypertrophy | 28 | (10) | 27 | (9) | 55/589 (9) | | .99 |
| (+)CSF cytocentrifuge with ≥5 cells/μL | 24 | (8) | 26 | (9) | 50/589 (8) | | .87 |
| Any extramedullary disease | 77 | (27) | 83 | (29) | 160/580 (28) | | .68 |
| Disseminated intravascular coagulopathy | 30 | (12) | 40 | (16) | 70/503 (14) | | .25 |
| Early deaths (≤10 d) | 3 | (1) | 2 | (1) | 5/589 (1) | | .85 |

and a significant increase in patients dying from toxicity, mainly infections, on the intensive arm ($P = .002$).

For patients receiving the intensive timing arm, the median time to completing cycles 1 and 2, with recovery of blood counts and a remission marrow when applicable, was 44 and 55 days for cycles 3 and 4, respectively. The total median time required to finish all four induction cycles before proceeding to postremission therapy was 99 days. For patients randomized to the standard timing arm, the median time to completing cycles 1 and 2 was 49 days. However, overall, the total median time required to finish all four induction cycles was 105 days, which was not statistically different from the time required for patients on the intensive timing arm ($P = .73$).

The major toxicity seen in the intensive timing arm was myelosuppression. Fever with neutropenia was almost universal, with bacteremia/septic episodes documented in 43% of all patients, compared with 24% in patients allocated to the standard arm ($P < .00001$). Increases in nonfatal toxicity were also seen in intensive timing patients in the lungs, kidneys, liver, and especially the gut (Table 3). However, all deaths on both arms were related to either infection or bleeding.

*Postremission phase.* For patients achieving remission, actuarial DFS results from the end of induction at 3 years (±95% confidence intervals [CI]) are as follows: coded regimen X, 34% ± 12%; coded regimen Y, 62% ± 10%; and coded regimen Z, 48% ± 11%. Overall actuarial survival results at 3 years are as follows: coded regimen X, 43% ± 13%; coded regimen Y, 70% ± 10%; and coded regimen Z, 58% ± 12%.

*Comparison of overall results: intensive timing versus standard timing induction.* Figure 2 shows the EFS from AML diagnosis for patients randomized to the intensive timing versus the standard timing arm. In the first 4 months of therapy (induction phase), there is no difference between the overall EFS for patients enrolled in the two induction arms. However, after that time, a clear superiority is shown for patients randomized to the intensive timing arm, with an overall 3-year actuarial EFS of 42% ± 7% versus 27% ± 7% for patients on the standard timing arm ($P = .0005$). Although overall survival at 3 years is not yet significantly

**Table 3. Induction Nonhematologic, NCI Grade 3-4 Toxicity (CCG-2891)**

| Affected Organ | Intensive Timing (N = 295) No. | (%) | Standard Timing (N = 294) No. | (%) | *P* Value |
|---|---|---|---|---|---|
| Gastrointestinal | 92 | (31) | 36 | (12) | <.00001 |
| Hepatic | 37 | (13) | 16 | (5) | .004 |
| Pulmonary | 28 | (10) | 12 | (4) | .01 |
| Genitourinary | 20 | (7) | 8 | (3) | .04 |
| Cardiac | 14 | (5) | 5 | (2) | .06 |
| Central nervous system | 3 | (1) | 8 | (3) | .22 |
| Infections | | | | | |
| Any | 213 | (72) | 153 | (52) | <.00001 |
| Bacteremia/sepsis | 127 | (43) | 71 | (24) | <.00001 |

different in the two arms (intensive timing 51% ± 7% *v* 39% ± 7% for standard timing patients, $P = .07$), survival advantage for the first year on study for the standard timing patients is subsequently lost and decreases with time (curves not shown).

For outcome of patients achieving remission, differences between those receiving intensive timing and standard timing induction are more dramatic. With a median follow-up of 28 months (range, 3 to 61 months), overall actuarial DFS 3 years from the end of induction for patients randomized to intensive timing induction (N = 212) is 55% ± 8%, versus 37% ± 8% for patients receiving standard timing (N = 195; Fig 3; $P = .0002$). Most of the adverse events in both arms were leukemia relapse rather than drug-related toxicity. Likewise, superior survival from achieving remission is documented at 3 years actuarial for the intensive timing patients (63% ± 9% *v* 47% ± 9%; $P = .01$).

Postremission outcome, based on therapy assigned, is shown in Table 4. Both DFS and overall survival are superior for patients receiving intensive timing compared with standard timing, irrespective of the type of allocated postremission therapy. *P* values for the intensive to standard timing comparison of DFS are .12 for coded regimen X, .008 for coded regimen Y, and .07 for coded regimen Z.

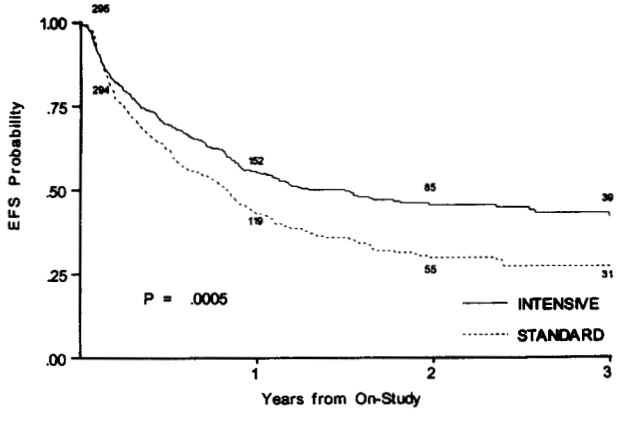



**Fig 2. EFS from time of study entry for patients with AML, comparing patients randomized to intensive induction timing versus standard induction timing. Intensive timing, N = 295; standard timing, N = 294.**

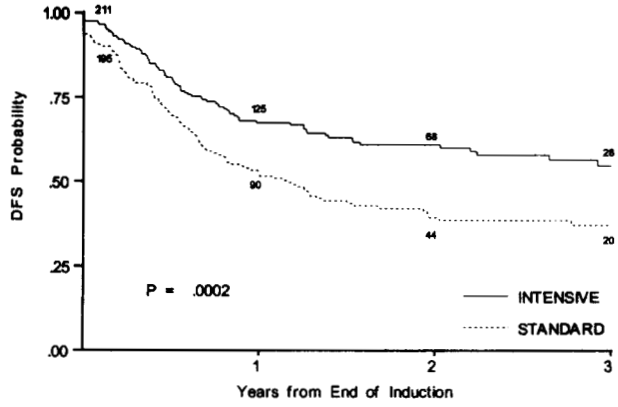



**Fig 3. DFS from the end of induction for patients with AML enrolled on CCG-2891 and achieving remission, comparing intensively timed induction with standard timed induction therapy. Intensive timing, N = 211; standard timing, N = 195.**

Analyses were performed to examine patient characteristics at diagnosis as potential confounders of the results obtained. In CCG AML trials over the last 15 years, the WBC has consistently been the most powerful prognostic factor, either in predicting induction success or long-term outcome.[1,3,24-26] Superior results are consistently found in the intensively timed patients within strata defined by WBC at AML diagnosis (≤20,000 or >20,000/μL). Similarly, neither age (0 to 2, 3 to 10, or 11+ years) nor the presence of extramedullary disease, including CNS leukemia, are significant confounders for the intensive versus standard timing comparison.

Finally, outcome for the standard timing-only patients was examined based on whether the second induction cycle was started within 18 days of cycle no. 1, indicating presence of significant residual leukemia on the day 14 BM, or started later, indicating that the first cycle had resulted in significant hypoplasia (approximately 60% of the patients). Had there been no effect of intensifying therapy early in the patients treated by day 18, one would have suspected a much worse prognosis for this group. Although there was a small advantage in EFS at 1 year for the patients receiving cycle 2 after day 18 (45% *v* 42%), by 3 years there was a slight but nonsignificant advantage for the standard timing patients who received an early second course (30% *v* 26%, $P = .51$, curve not shown). Hence, intensifying therapy by timing for patients with a poor initial response to induction improves this group's outcome.

## DISCUSSION

Intensity of cancer chemotherapy is an important variable that is still poorly understood. Early in vitro work by Skipper et al[29] and Frei and Canellos[30] documented a dose-response effect that was often logarithmic; with each doubling of in vitro exposure doses of active agents, more than a logarithm increase in cell kill was found.

**Table 4. Three-Year Actuarial Survival and Disease-Free Survival (±95% CI) From the End of Induction Therapy (EOI) for Patients With AML Based on Allocated Induction and Postremission Regimen**

| | Disease-Free Survival From EOI | | | Survival From EOI | | |
|---|---|---|---|---|---|---|
| Postremission Therapy | Intensive Induction | Standard Induction | *P* Value | Intensive Induction | Standard Induction | *P* Value |
| Coded regimen X | 0.36 ± 0.17 | 0.30 ± 0.15 | .12 | 0.47 ± 0.20 | 0.37 ± 0.19 | .28 |
| Coded regimen Y | 0.77 ± 0.12 | 0.49 ± 0.15 | .008 | 0.83 ± 0.11 | 0.58 ± 0.15 | .01 |
| Coded regimen Z | 0.58 ± 0.16 | 0.40 ± 0.14 | .07 | 0.65 ± 0.16 | 0.54 ± 0.15 | .34 |
| All patients (N = 383) | 0.55 ± 0.09 | 0.37 ± 0.08 | .0002 | 0.63 ± 0.09 | 0.47 ± 0.09 | .01 |

In vivo, one can increase chemotherapy intensity by several methods. These include increasing (1) the number of drugs used in a cycle, (2) the total doses of drugs in a cycle, (3) the frequency of cycles, or (4) the total number of cycles administered. Response by different types of neoplasms to various types of intensity will clearly vary. For example, in small noncleaved (Burkitt's) non-Hodgkin's lymphoma of childhood, increasing doses of active drugs early in the treatment course appears to have beneficial long-term effects.[31,32] In adult breast cancer, a recent randomized trial showed that women receiving twice the dose intensity, either by increasing the drugs per course or increasing the total number of courses, had improved long-term DFS.[33]

In AML, increasing the doses of active drugs used during induction therapy has slowly increased induction success rates in the past 25 years to a plateau of 70% to 85%. Long-term outcome improves with more aggressive postremission therapy.[2-5,8,34] Whether a more intensive approach for AML at diagnosis would change overall outcome has only been investigated in a preliminary fashion.[35,36] Several previous studies have documented that increasing the intensity of chemotherapy during induction often leads to similar remission rates, with different reasons for failing to achieve remission noted. More aggressive regimens increased therapy-associated mortality, whereas less aggressive regimens that lower toxicity-related deaths have been associated with increased leukemia nonresponsiveness.[3,5,6] Furthermore, addition of active drugs over the use of an anthracycline and cytarabine combination has not apparently changed either induction success or outcome.

To further define the above clinical observations as well as the potential for maximizing in vivo leukemic cell kill by recruitment and synchronization of residual cells by chemotherapy, we embarked on this therapeutic trial, CCG-2891. The only induction variable was the timing of chemotherapy to be administered. Patients randomized to intensively timed induction therapy received two cycles of therapy 10 days apart, with an additional two cycles administered in an identical fashion once hematologic parameters had recovered. Patients randomized to standard timing received the second and subsequent cycles of chemotherapy 14 days or later from initiating the preceding cycle. This approach is commonly used by adult and pediatric oncologists worldwide. Furthermore, the standard timing induction regimen was quite similar to that in the previous CCG study, CCG-213,[3] in which the identical five drugs were used at less or equal doses to the current regimen, with an induction rate and long-term outcome equal to or better than any previous CCG AML study.[3,25] Hence, the standard timing arm represents adequate therapy for AML.

Although the overall time necessary to administer all four induction cycles was the same in the two randomized regimens (99 days for intensive timing versus 105 days for standard timing patients) and all patients received the identical number of cycles, there was a clear advantage in long-term outcome for patients receiving the intensively timed cycles. Before initiating CCG-2891, it was anticipated that improved leukemic cytoreduction would be compounded by an increased number of toxic deaths.[37] As expected, a difference in induction success was not observed. However, postremission outcome was dramatically improved for intensively timed patients, suggesting a greater decrease in leukemia cell burden during the induction phase. In childhood acute lymphocytic leukemia (ALL), increasing induction intensity by increasing the number of active cytotoxic agents used has been shown to improve long-term outcome, even though changes in induction success are minimal.[38,39] Hence, a more intensive approach to AML induction has a major positive effect on ultimate EFS and survival. Except for myelosuppression and to a lesser extent gastrointestinal morbidity, toxicity noted in the CCG-2891 intensive timing arm was only slightly worse than previous CCG AML trials and did not contribute to the high induction death rate. Other investigators have used equally myelosuppressive regimens in adults with AML, sometimes in a timed sequential fashion.[5,17,18,40] Although induction toxicity in adults is generally greater than that in children,[2-6] the induction approach described herein should be feasible in young and middle-aged adults.

The use of myeloablative therapy followed by allogeneic BMT rescue is one of the most important ways to improve long-term survival in AML patients achieving remission.[9,10,25] Various studies have touted specific preparative regimens, with long-term survival for AML patients in first remission between 50% and 80%.[9,10,41-45] In the current study, with more than 300 patients allocated or randomized to one of the three postremission arms, there is a dramatic improvement in DFS from the end of induction for patients who initially received intensive induction timing, irrespective of the type of allocated postremission therapy (Fig 3 and Table 4). Even though the three postremission arms remain coded, there is a clear outcome advantage for patients receiving intensive timing induction therapy who subsequently also received myeloablative therapy followed by BMT rescue.

Without controlling for the type of induction therapy received, results of various BMT studies in AML comparing different preparative regimens will be most difficult to interpret. BMT investigators are encouraged to participate more with national cooperative groups in which the type of induction therapy is controlled in a large number of patients.

Overall, the results of this AML trial are very encouraging. Patients receiving aggressive induction therapy, such as the timed sequential approach described herein, can be expected to have a 3-year EFS from diagnosis which approaches 50%, with an equal number expected to survive long term. Although adults can in general be expected to have more treatment-related toxicity than children,[2-6] the lessons learned from this therapeutic trial should benefit young and middle-aged adults as well as children. Future advances in AML treatment will probably come not just from improving the antileukemia therapy used, but also from learning to more deftly manage the major sequelae of myelosuppressive chemotherapy, namely opportunistic infections.

## NOTE ADDED IN PROOF

A recent analysis of overall survival from diagnosis now documents a statistically superior outcome for all patients randomized to the intensive timing arm. Actuarial survival at 3 years for intensive timing patients is 52% ± 6% versus 42% ± 6% for standard timing patients (and at 5 years, 49% ± 6% *v* 38% ± 6%, respectively; $P = .04$).

## APPENDIX

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